Remark

Claims 1, 13 and 19 are amended herein to clarify that the disclosed methods concern determination of haplotypes encompassing a coding locus using, at least in part, sequence variations in genetically linked non-coding regions. The amendment is supported in the specification at least at pg. 7, lines 16-19; pg. 7, line 33 through pg. 8, line 3; and pg. 9, lines 4-7.

Claims 1, 8, 13 and 19 are amended herein to clarify that a haplotype may encompass one or more genetic loci. Support for the amendment is found in the specification at least at pg. 9, lines 22-28, which states that, " As used herein, 'haplotype' is a region of genomic DNA on a chromosome which is bounded by recombination sites such that genetic loci within a haplotypic region are usually inherited as a unit. However, occasionally, genetic rearrangements may occur within a haplotype. Thus, the term haplotype is an operational term that refers to the occurrence on a chromosome of linked loci." That definition makes clear that a "haplotype" may include multiple genetic loci.

Claim 8 is amended herein to clarify that the disclosed methods may utilize sequence variations in coding regions in addition to sequence variations in non-coding regions to determine haplotypes encompassing a coding locus. The amendment is supported in the specification at least by original claim 12 and by the specification at least at pg. 8, lines 4-6 which recites that "intron sequences provide genetic variations that, in addition to those found in exon sequences, further distinguish sample DNA...." (emphasis added) Additionally, pg. 16, lines 13-16 specifies that the amplified sequence to be analyzed "preferably includes at least a portion of one of the introns adjacent to a

variable exon and can include a portion of the variable exon. When additional sequence information is required, the amplified DNA sequence preferably encompasses a variable exon and all or a portion of both adjacent intron sequences."

New claims 31-46 are added herein. Support for the amendments may be found in the specification at least as follows. Claim 31 is supported at least by claim 1 of USSN 07/949,652 (issued U.S. Patent No. 5,612,179) as well as the Specification at least at pg. 7, line 15 through pg 8, line 11; pg. 8, lines 18-22; pg. 8, lines 28-31; pg. 10, line 29 through pg. 11, line 8; and pg. 75, line 2 through pg. 79, line 2. Claim 32 is supported in the Specification at least at pg. 75, line 1 through pg. 79, line 2. Claim 33 is supported in the Specification at least at pg. 4, line 2. Claim 34 is supported by at least by claim 15 of USSN 07/949,652 (issued U.S. Patent No. 5,612,179) as well as the Specification at least at pg. 8, line 7; pg. 75, line 12 through pg. 77, line 2 and pg. 78, line 31. Claim 35 is supported by the Specification at least at pg. 8, line 7 and pg. 78, line 31. Claim 36 is supported in the Specification at least at pg. 39, line 5 through pg. 40, line 14. Claim 37 is supported in the Specification at least at pg. 39, lines 21-28 and pg. 40, lines 3-14. Claim 38 is supported in the Specification at least at pg. 20, lines 6-11. Claim 39 is supported in the Specification at least at pg. 39, line 5 through pg. 40, line 14.

Claim 40 is supported at least by claim 26 in USSN 07/949,652 (issued U.S. Patent No. 5,612,179) as well as the Specification at least at pg. 9, lines 27-34; pg. 14, lines 25-29 and pg. 15, lines 12-14. Claim 41 is supported in the Specification at least at pg. 7, line 30; pg. 19, lines 33-35 and pg. 20, lines 8-11. Claim 42 is supported in the Specification at least at pg. 7, lines 33-36 and pg. 12, lines 15-21. Claim 43 is supported

in the Specification at least at pg. 14, lines 29-33 and pg. 76, lines 22-25. Claim 44 is supported in the Specification at least at pg. 76, lines 22-25; pg. 77, line 30 through pg. 78, line 4 and pg. 78, lines 17-23. Claim 45 is supported in the Specification at least at pg. 10, line 29 through pg. 11, line 8 and pg. 17, lines 5-19. Claim 46 is supported in the Specification at least at pg. 16, lines 18-22; pg. 75, lines 7-11 and pg. 76, lines 25-28.

Applicant submits that no new matter is added herein and requests entry and consideration of the amended claims. Applicant notes that claims 31-46 represent subject matter that was recited in co-pending U.S. Patent Application Serial No. 10/005,626, filed December 3, 2001. For efficiency of prosecution, Applicant is expressly abandoning USSN 10/005,626 and adding those claims to the instant application.

Applicant further notes that a final Office Action ("the Action") was mailed on October 27, 2000 in USSN 09/070,497, the parent case of the instant application. Although the claims prosecuted in USSN 09/070,497 are not pending in the instant application, to expedite prosecution Applicant addresses certain issues raised in the Action.

Rejection Under 35 U.S.C. §102/103

Claims 34-37 of USSN 09/070,497 were rejected under 35 U.S.C. §102(b), or in the alternative §103, over the reference of Frossard (U.S. 4,772,549).

Rejection of claims under §102 is improper unless each and every element of the claimed subject matter is found, either expressly or inherently described, in a single prior art reference. [*Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628,631 (Fed. Cir. 1987(; MPEP §2131.] Instant claim 1 recites, "amplifying genomic DNA, wherein

the amplified genomic DNA comprises a non-coding region sequence that is in genetic linkage with the genetic coding locus...." Instant claim 13 recites, "amplifying genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said genetic coding locus and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said at least one haplotype...." Instant claim 19 recites, "amplifying genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said HLA coding locus...." Instant claim 31 recites, "amplifying a non-coding region of genomic DNA with a primer pair to produce an amplified DNA sequence, wherein said non-coding region is in genetic linkage with one or more coding region alleles that confer a trait...." Each of the claims comprises an element of amplifying genomic DNA. Applicant submits that element is nowhere taught, and is not even suggested, in the reference of Frossard. Therefore, rejection of the instant claims under §102 over Frossard would be improper.

The Action states that, "For purposes of examination, the claimed method has been interpreted as encompassing any method of identifying one or more genetic variations in a genomic DNA sample." Applicant submits that this is a gross mischaracterization of the claimed invention. "Any method of identifying one or more genetic variations in a genomic DNA sample," would read on the first detection of a genetic variation, a process that arguably goes back to Mendel's time and at least dates to Watson and Crick's elucidation of the structure of DNA.

All of the pending claims of the instant application comprise amplifying genomic DNA comprising a non-coding region in genetic linkage with a coding locus and/or coding region allele; detecting genetic variation in the non-coding region; and using the non-coding variation to determine something about the genetically linked coding regions, either determining haplotypes or correlating the non-coding region variations with traits conferred by coding region alleles.

Thus, it is not identification of <u>any</u> genetic variation in genomic DNA that falls within the scope of the claims. Rather, the genetic variations must be in non-coding regions, the non-coding regions to be analyzed must be amplified, the non-coding regions must be in genetic linkage with one or more coding regions, and the non-coding region variations must provide some information about the genetically linked coding regions.

Applicant submits that Frossard does not teach or even remotely suggest such a method. Nowhere does Frossard suggest amplification of a non-coding region of genomic DNA. The polymorphisms characterized by Frossard are summarized in Table I (columns 11 and 12). The locations of the polymorphisms, with one exception, are indicated as unknown (i.e., Frossard didn't even know if he was looking at coding or non-coding region polymorphisms). In the one instance of Table I where Frossard identified a polymorphism as occurring in a non-coding location (2 kb 3' of apoCII gene), he stated that that polymorphism was not correlated with a phenotypic trait. Further, there was no indication whatsoever in Frossard that the non-coding region polymorphism (2 kb 3' of apoCII gene) was in genetic linkage with one or more coding regions.

In order to establish a prima facie case of obviousness, the cited prior art reference (or references when combined) must teach or suggest all the claim limitations. [MPEP §2142] Applicant submits that since the reference of Frossard neither teaches nor suggests amplifying a non-coding region of genomic DNA to produce an amplified DNA sequence, and no other prior art reference is cited by the Action, a prima facie case of obviousness has not been established.

Assuming for the sake of argument that a reference disclosing amplification of genomic DNA had been cited by the Action, Applicant submits that a prima facie case of obviousness would still not exist. Another requirement for a prima facie case of obviousness is some suggestion or motivation to modify the reference or combine the reference teachings. No suggestion or motivation has been cited in any prior art document of record to suggest the combination of amplifying non-coding regions of genomic DNA to produce amplified DNA sequences, wherein the non-coding regions are in genetic linkage with one or more coding regions; analyzing the amplified DNA sequences to detect non-coding region variations; and using the non-coding region variations to determine haplotypes encompassing coding region loci or correlating them with traits conferred by coding region alleles. Applicant respectfully submits that such combination could only be derived by hindsight reconstruction of Applicant's own disclosure.

For the reasons stated above, Applicant respectfully submits that the pending claims are allowable over the prior art and requests a finding of allowable subject matter.

Charge our Deposit Account

Please charge any shortage to our Deposit Account No. 02-2666.

Respectfully submitted,

BLAKELY, SOKOLOFF, TAYLOR & ZAFMAN LLP

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